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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/799,162

03/12/2004

David G. Winkler

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06/01/2006

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EXAMINER

XIE, XIAOZHEN

ART UNIT

PAPER NUMBER

1646

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/799,162	Applicant(s) WINKLER ET AL.	
	Examiner Xiaozhen Xie	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) 6-17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 December 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>20040716,20041207</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Information Disclosure Statement (IDS) filed 16 July 2004 and 7 December 2004 has been entered in full.

Applicant's election of Group I, claims 1-5, in the reply filed on 13 April 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 6-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-17 are pending. Claims 1-5 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 3 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to an isolated complex comprising a first and a second TGF- β binding protein in a specific association, wherein a) the first TGF- β binding protein is capable of binding a first TGF- β superfamily member that is a first cognate ligand; and b) the second TGF- β binding protein is capable of binding a second TGF- β superfamily member that is a second cognate ligand; wherein the complex is incapable of binding the first or either of the first and second cognant ligand. What applicant has described in the specification is an isolated complex of sclerostin-noggin or sclerostin-chordin, wherein sclerostin, noggin and chordin are BMP antagonists which are able to bind to different TGF- β superfamily member, such as BMPs. Applicant has not described isolated complexes comprising other TGF- β binding proteins, wherein the interaction between the TGF- β binding proteins is competitive and exclusive of each other's ligand binding. There is no teaching regarding the relationship of structure to function. Thus, the claims encompass a genus of molecules, which vary substantially in composition, and could have very different structural and functional characteristics from the polypeptide that Applicant has disclosed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making of the claimed product, or any combination thereof. In this case, there is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient

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recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of peptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated complex comprising sclerostin and noggin, or sclerostin and chordin, but not the full scope of the claimed complexes comprising a first

and a second TGF- β binding protein in a specific association, is adequately described in the disclosure.

Claims 2 and 3 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated complex comprising sclerostin and noggin, or comprising sclerostin and chordin, does not reasonably provide enablement for other isolated complexes comprising other TGF- β binding proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are directed to an isolated complex comprising a first and a second TGF- β binding protein in a specific association, wherein a) the first TGF- β binding protein is capable of binding a first TGF- β superfamily member that is a first cognate ligand; and b) the second TGF- β binding protein is capable of binding a second TGF- β superfamily member that is a second cognate ligand; wherein the complex is incapable of binding the first or either of the first and second cognate ligand. The claims are broad in that they encompass complexes comprising any two of TGF- β binding proteins. The specification discloses an isolated complex of sclerostin-noggin or sclerostin-chordin, wherein sclerostin, noggin and chordin are BMP antagonists which are able to bind to different TGF- β superfamily members, such as BMPs, and the interaction between sclerostin and noggin, or between sclerostin and chordin, blocks the BMP antagonist activity of each other. The specification discloses that compositions comprising such

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complexes are useful in therapeutic strategies that relate to influencing bone mineralization, for instance in osteoporosis. The specification, however, does not provide any guidance for making or using other isolated complexes comprising other TGF- β binding proteins which possessing the same property. There is no teaching regarding the relationship of structure to function. TGF-b binding proteins encompass a genus of molecules with diverse structure and exerting a wide spectrum of biological responses on a large variety of cell types in both vertebrates and invertebrates. For example, latent TGF- β binding protein-1 (LTBP1) which binds and regulates TGF- β , exhibits an completely different effect from noggin (Sivakumar et al., 2006, J cell Sci., 119(7):1350-1360, see Introduction). Further, not all TGF- β binding proteins are identified. For natural occurring BMP antagonists, Balemans and Van Hul (Dev. Biol., 2002, 250:231-250) teach that an increasing number of these natural antagonists are being identified in vertebrates and inveterbrates (pp. 235, left column, 2nd paragraph).

Since the specification does not define the chemical structures for all claimed complexes, one of skill in the art would evaluate all non-exemplified TGF- β binding protein complexes for ligand binding and antagonist activities. Thus, undue experimentation would be required for the artisan to make and use the invention as broadly claimed.

Due to the large quantity of experimentation necessary to generate the nearly infinite number of complexes comprising a first and a second TGF- β binding protein in a specific association recited in the claims and screen same for ligand binding and antagonist activities, the lack of direction/guidance presented in the specification

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regarding which structural features are required in order to provide activities, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of protein structure on function, and the breadth of the claims which fails to recite any structural limitations and encompasses all TGF-binding proteins, known or unknown, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 are indefinite for the recitation of "in specific association". It is unclear what specific association the claims intend to encompass. Claims 4 and 5 are rejected for depending upon a rejected claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Grainger et al. (U. S. Patent No: 6,117,911). The '911 patent teaches a complex comprising a first and a second TGF- β binding proteins, the latency associated peptide (LAP) and the TGF- β binding protein (LTBP-1), wherein both proteins are capable of binding to TGF- β (the ligand), and once the complex is formed, TGF- β can be activated, i.e., TGF- β dimer without the binding proteins (Figure 1 and legend in column 7, lines 41-54). Therefore, the '911 patent anticipates the claimed invention.

Conclusion

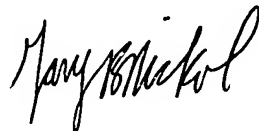
NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph. D.
May 23, 2006



**GARY B. NICKOL, PH.D.
PRIMARY EXAMINER**